

AMENDMENT

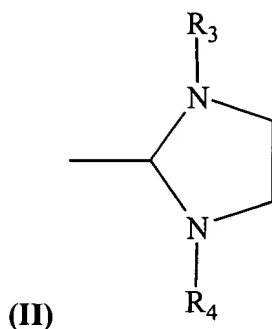
In the Specification

1. On page 2, replace lines 17-23 with

B1
The present invention comprises highly active and recyclable transition metal-based metathesis catalysts, methods of making such catalysts and their use in metathesis reactions. The catalysts of the present invention are organometallic complexes of a transition metal comprising an organic ligand that permits recovery of the catalyst metal from the reaction mixture. The organometallic complexes of the invention can be in monomeric, polymeric and dendritic forms that are capable of promoting various forms of metathesis reactions in a highly efficient manner, and can be efficiently recovered from the reaction mixtures and reused; they are therefore,

2. On page 4, replace lines 5-15 with

B2
In a preferred embodiment, M is ruthenium, X is O, R is a lower alkyl group (e.g., C₁-C₁₂), R₁ and R₂ are halogen atoms (which may be identical or different but preferably are identical), a, b, c and d each comprises hydrogen or a lower alkyl group (e.g., C₁-C₁₂), and Y comprises a 4,5-dihydroimidazol-2-ylidene carbene ligand ring structure or a phosphine moiety. In a more preferred embodiment, M is ruthenium, X is O, R is isopropyl, R₁ and R₂ are chlorine atoms (Cl), a, b, c and d each comprises hydrogen, and Y comprises a heterocyclic ring structure having the following Formula II:



wherein R₃ and R₄ comprise the same or different aromatic ring moieties. In a currently preferred embodiment, R₃ and R₄ both comprise 2,4,6-trimethylphenyl (mesityl) moieties.

3. On page 8, replace lines 4-8 with

Figure 3 shows the transition metal catalysts (1, 2) and organometallic compound 3 comprising an active metal complex.

153
Figure 4 shows surface immobilized catalysts of the invention coupled to a solid phase (represented by a spherical solid substrate) via different types of linkers.

4. On page 9, replace lines 10-13 with

154
Monomeric complexes. In one aspect, the present invention provides monomeric catalysts having the structure shown as Formula I. Monomeric catalysts having Formula I can be prepared according to the procedures shown in Equation 1 below, in Examples 1-10, or via other synthetic routes that would be readily ascertainable by those skilled in the art.

5. On page 11, delete lines 5-8.

6. On page 12, delete lines 1-8.
7. On page 12, replace lines 9-15 with

Catalytic Activity and Recovery of Formula 5 catalyst. The data in Table 2 below

B5
illustrate that the Formula 5 catalyst is an effective catalyst for RCM of dienes. In this reaction, hetero- and carbocyclic compounds bearing trisubstituted alkenes were obtained from the corresponding precursor dienes in the presence of 5 mol % catalyst at ambient temperature within 10 min. to 2 h. As shown in entries 1 and 2 of Table 2, both 1,1-disubstituted (7) and trisubstituted olefins (9) may be utilized in the synthesis of trisubstituted cyclic alkenes. The catalytic RCM in entries 3-4 indicate that trisubstituted allylic alcohols (12) and acetates (14) can

8. On page 13, replace lines 1-5 with

B6
be accessed in the presence of 5 mol % 5 within 2 h. The Ru catalyst of Formula 5 is recovered with high efficiency (95% and >98% yield, respectively). The prior art catalyst 1 is significantly less efficient in promoting the above transformations. As an example, treatment of structure 11 with 5 mol % 1 (22°C, CH₂Cl₂) leads to only 15% conversion after 2 h (as judged by 400 MHz ¹H NMR).

9. On page 13, replace lines 7-13 with

B7
(1) In all instances, the catalyst is recovered, along with the desired cyclic product in high yield after simple silica gel chromatography. Moreover, addition of 2 equivalents of styrene ether 4 (relative to the catalyst) to a solution of a transformation promoted by the non-recyclable 3 at the end of the reaction time, leads to the isolation of the recyclable catalyst 5. As an

B7
entire
example: Treatment of diene carbinol 11 is treated with 5 mol % 3 (CH_2Cl_2 , 22°C , 1 h), followed by the addition of 10 mol % 4 and addition stirring for 1 h, leads to the formation of 12 and 5 in 98% and 82% yields, respectively (after silica gel chromatography).

10. On page 14, replace lines 1-3 with

B8
^aConditions: 5 mol % 5 for entries 1 and 3-6, 1 mol % 5 for entry 2, 22°C , CH_2Cl_2

(entries 1-4); 24 h at 22°C and 20 h at 40°C , CH_2Cl_2 for entry 5; toluene, 80°C for entry 6.

^bIsolated yields after silica gel chromatography.

11. On page 17, replace lines 5-10 with

B9
a. anhydrous HCl , $i\text{-PrOH}$, >87%, b, 2 equiv NaH , 2 equiv $i\text{-PrI}$, DMF , THF , 89%. c. 1.1 equiv Br_2 , HOAc , CH_2Cl_2 , 98%. d. 1.1 equiv $\text{Bu}_3\text{SnCHCH}_2$, 3 mol % $\text{Pd}(\text{PPh}_3)_4$, 2 mol % BHT , tol , 110°C , 4h, >98%. g. 4.3 equiv HMe_2SiCl , 5 mol % H_2PtCl_6 in THF , 3h. h. 4.2 equiv $\text{CH}_2\text{CHCH}_2\text{MgBr}$, Et_2O , 22°C , 3h, >90% overall for two steps. i. 5.1 equiv 9-BBN, THF , 22°C , 17 h; NaOH , H_2O_2 , EtOH , THF , 22°C , 6 h, 96%. J. 4.9 equiv $\text{EDC}\cdot\text{HCl}$, 4.5 equiv 26, 0.6 equiv DMAP , 22°C , 3 h, 63%. k. 4.3 equiv 2, 4.6 equiv CuCl , CH_2Cl_2 , 22°C , 3 h, 83%.

12. On page 18, replace lines 1-6 with

B10
The key features of the synthesis shown in Scheme 4 include the attachment of the requisite vinyl group through a palladium (Pd)-catalyzed Stille coupling ($\rightarrow 26$) and preparation of the dendrimer backbone by a platinum (Pt)-catalyzed hydrosilation / alkylation / hydroboration sequence ($27 \rightarrow 28 \rightarrow 29$). Coupling of 29 with four equiv 26, followed by

B10
incorporation of the Ru center through treatment with 2 in the presence of CuCl affords the
desired 30 as an air stable brown solid (mp = 92-98 °C dec.).

13. On page 19, replace lines 1-8 with

Catalytic RCM, ROM and CM Promoted by Dendritic Catalysts of Formulas 30

B11
and 31. Table 3 below illustrates the use of the present dendritic catalysts in a RCM reaction. As shown in Table 3, treatment of diene 32 with 1.25 mol % of 30 (5 mol % Ru) leads to efficient and catalytic RCM. The desired product (33) is first isolated in 99% yield by silica gel chromatography through elution with CH₂Cl₂ subsequent wash of the silica with Et₂O leads to the isolation of the dendritic catalyst (>98% mass balance). Recovered 30 was analyzed by 400 MHz ¹H NMR spectroscopy; the resulting spectrum indicated that 13% of the styrenyl ligands were vacant (approximately 13% Ru loss).

14. On page 20, replace lines 5-18 with

B12
As illustrated in Table 3, repeated use of Formula 30 as a catalyst results in complete conversion of 32 to 33 and isolation of the desired product in >86% isolated yield. These data thus illustrate that dendrimer 30 is effective in promoting the catalytic RCM of terminal dienes in a highly efficient manner, and can be easily recovered by simple silica gel filtration and reused repeatedly in subsequent reactions. In addition, after repeated use, the partially depleted dendrimer complex can be easily re-metalated upon treatment with the appropriate equivalents of 2 and CuCl in CH₂Cl₂. The dendritic complex remains active even after nearly 50% of the

B12
b7d
Ru content has been depleted (see cycle 6 in Table 3). This level of reactivity may be attributed, at least partially, to the fact that 30 (similar to monomeric catalysts 1 and 5) releases a highly active mono-phosphine Ru complex into the solution. In the absence of a second equivalent of PCy₃ that can re-coordinate to Ru and retard its catalytic activity (which is the case when 2 or 3 are used as catalysts), and since styrene ethers probably do not kinetically re-associate with Ru as efficiently as PCy₃, even a small amount of Ru release can lead to substantial amounts of metathesis activity.

15. On page 21, replace lines 1-15 with

B13
Metal crossover experiments were carried out as depicted in Scheme 5. Treatment of compound 4 with dendritic Ru complex of Formula 30 results in little or no metal crossover (<2% 1 formed by 400 MHz ¹H NMR analysis). The amount of Ru bound to the dendritic vs monomeric ligands is readily determined by the chemical shift difference in the ¹H NMR spectra of the corresponding carbene CH (Ru=C(H)). When diene substrate 32 is treated with 1.25 mol % fully loaded 30 and 4 mol % 4, RCM product 33 is obtained within 15 mm. However, recovered 30 bears 42% less Ru, compared to 13% metal reduction when the reaction is carried out in the absence of 4 (see Table 3, cycle 1). In addition, ~30% of uncomplexed 4 is isolated after the reaction; the remainder of the monomeric styrenyl alkoxide is recovered as monomeric Ru complex 1. These observations indicate that the Ru metal, after reacting with the diene substrate and leaving the dendrimer, can be trapped again by a styrenyl alkoxide. Thus, in the absence of compound 4, the catalytically active Ru monophosphine would likely return to a styrene unit within the dendritic structure.

16. On page 22, replace lines 3-12 with

B14
Dendrimer 31 exhibits catalytic activity higher than that observed for 30. Unlike 1 or 30, but similar to 5, dendritic 31 efficiently promotes the formation of trisubstituted allylic alcohol 12 (Scheme 4); in addition to the desired product (78%), the dendrimer is recovered after silica gel chromatography quantitatively with 8% loss in Ru loading (judged by analysis of 400 MHz ¹H NMR). Moreover, as shown in Equation (5), similar to 5, dendrimer 31 effectively catalyzes tandem ROM / RCM of 19 and the formation of 20 (94%). However, in contrast to the corresponding monomer 5, dendrimer 31 can be easily separated from 20 and recovered in 90% yield (8% Ru loss). The transformation in **Scheme 6** indicates that 31 effectively promotes catalytic ROM / CM reactions as well, and as before, it can be recovered readily and in good yield (>98% trans olefins in 22 and 34, as judged by 400 MHz ¹H NMR analysis). Thus,

17. On page 23, replace lines 3-6 with

B15
Similar to monomeric 5, lower loadings of 31 are sufficient for efficient catalytic metathesis. As an example, when triene 7 is treated with 0.25 mol % 31 (CH₂Cl₂, 22°C) for 10 min, RCM adduct 8 is formed with >98% cony. In addition to dihydrofuran 8, isolated in 84% yield, recovered 31 is obtained in 88% yield after silica gel chromatography (22% Ru loss).

18. On page 24, replace lines 6-23 with

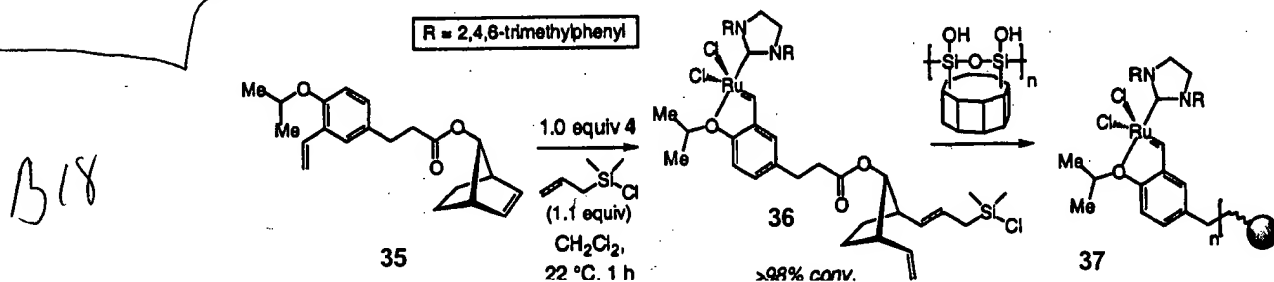
B16
The surface immobilization of the catalysts to solid phase substrates involves a preliminary step wherein the catalysts are chemically reacted with an organic coupling agent to provide adducts that are capable of chemically bonding to said solid phase substrates. In a

b16
preferred embodiment, the said adduct contains a silyl functionality that enables surface immobilization on solid phase substrates via chemical bonding of the silyl group to the said substrates. In a most preferred embodiment the catalysts of the invention are coupled to the organic linker and functionalized with a silane-containing moiety in a single step. Surface immobilization of the said silane modified compounds onto solid phase substrates is accomplished in-situ by subsequent addition of said substrate into the reaction vessel. Preferred coupling agents are norbornene derivatives that are capable of reacting with catalysts of the invention, and further capable of reacting with organo-silane agents to provide silyl-functionalized derivatives that may be used in surface immobilization reactions. Preferred solid phase substrates include those capable of chemically reacting with the silyl moiety. In a most preferred embodiment, the solid phase substrate is a porous glass monolith having preferably an average pore size of about 200 Å. More specifically, as shown in **Scheme 7**, a ring-opening reaction combined with cross metathesis of anti-norbornenol ester **35** in with 1.0 equivalent each of organometallic complex **3** and allylchlorodimethylsilane (0.05 M CH₂Cl₂, 22 °C) proceeds to >98% conversion in <1 h to give adduct **36** (analyzed by 400 MHz ¹H NMR). Surface

19. On page 25, replace paragraph 1 (lines 5-8) with

b17
In other preferred embodiments, surface immobilized catalysts **38** and **39** shown in **Figure 4** are obtained in an analogous fashion from the corresponding norbornene substrates. Surface immobilized catalysts **37**, **38** and **39** were evaluated for catalytic activity, recovery and recyclability.

20. On page 25, replace Scheme 7 with



Scheme 7

21. On page 26, replace lines 3-4 with

B19

The surface immobilized catalysts of the present invention provide the following advantages over non-immobilized catalysts 1 and 2 and 3 (Figure 3).

22. On page 27, replace lines 1-13 with

B20

(3) After four consecutive rounds of RCM utilizing surface immobilized catalysts with different organic linker types, the respective gel pellets after thorough drying in vacuo and subsequent weighing yielded mass differences that are highly reproducible, indicating a net metal loss of between 20 to 25% over the four reaction cycles. Despite this significant drop in Ru catalyst loading relative to the initial values, the catalytic activities of the recovered, recycled gel pellets remain high. Absence of cross-contamination of reaction products by surface immobilized catalysts of the present invention may be demonstrated by using the same samples for the ring-opening metathesis (ROM) of 7-anti-norbornenol in the presence of a variety of donor olefins, including highly electron-rich olefins such as vinylferrocene. As shown in Table

5, productive metathesis for three additional rounds of norbornenol **42** occurred in <1 h to yield ring-opened compound **43**. The Ru-containing impurities, as well as the product of the previous RCM reaction **41** could not be detected by NMR spectroscopy (400 MHz ¹H NMR analysis) of the corresponding unpurified reaction product mixtures.

23. On page ~~30~~, replace line ~~1-10~~ with

an atmosphere of argon. (PCy₃)₂Cl₂RuCHPh (**Formula 2**) was prepared according to literature procedures.³⁰ (4,5-dihydrolMES)(PCy₃)Cl₂Ru=CHPh (**Formula 3**) and its requisite starting materials were prepared by a modification of the published method³¹ (see below for further details). 2-isopropoxystyrene was prepared by alkylation and Wittig olefination. All other materials were obtained from commercial sources and purified before use. Tetrahydrofuran, diethyl ether, benzene, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, pentane, hexanes, 2-propanol, triethylamine, and ethanol were distilled from calcium hydride under Ar. Methanol was distilled over Mg under Ar. 2,4,6-trimethylaniline was vacuum distilled. Triethyl orthoformate (Aldrich) was distilled from MgSO₄ under reduced pressure. 3-(4-Hydroxyphenyl)-propionic acid (Aldrich) was recrystallized from water. 2-

24. On page ~~31~~, replace lines ~~6-16~~ with

All silica gel column chromatography was driven with compressed air and performed with silica gel 60 (230-400 mesh; pH (10% suspension) 6.5-7; surface area 500 m²/g; pore volume 0.75 ml/g) obtained from TSI Chemical Co. (Cambridge, MA). Similar to the original monomer **1**, dendritic catalyst **30** forms a dark brown solution in organic solvents. In contrast, the more active catalysts bearing the 4,5-dihydrolMES ligand form bright green-colored organic

B22
added

solutions. The purification of the above complexes can be easily monitored visually since they appear as dark brown or green-colored bands on the column. Dendritic complexes 30 and 31 are significantly more polar than the corresponding monomers. Following a metathesis reaction mediated by 30 or 31, isolation of both product and catalyst typically involved simply a filtration of the crude mixture through a silica gel plug in 100% CH₂Cl₂ followed by a column "flush" in 100% Et₂O (TLC R_f of 30 and 31 < 1.0 in CH₂Cl₂).

25. On page 32, replace lines 11-23 with

B23

Example 2: Synthesis of ((2,4,6-Trimethylphenyl)NHCH₂)₂. The bis(imine) ((2,4,6-trimethylphenyl)NCH) (7.30 g, 25.0 mmol) was suspended in 250 mL of MeOH in a 500 mL round-bottom flask. Several crystals of bromocresol green were added as a pH indicator and the mixture was cooled to 0 °C. NaCNBH₃ (10.0 g, 159 mmol, 6.4 equiv) was added to the reaction mixture in one portion as a solid. Vigorous bubbling was observed and the reaction mixture turned a deep blue-green color (alkaline pH). After 10 mm concentrated HCl was added dropwise to the mixture, restoring its original yellow color. Additional reduction slowly occurred, causing the mixture to again become basic. The acidification process was repeated (typically two more times) until the yellow color persisted. The reaction mixture was warmed to 22 °C and stirred for 1 h. A solution of 2 M KOH was added dropwise until the mixture was weakly alkaline (pH = 8-9). The mixture was then diluted with water (300 mL), transferred to a separatory funnel, and washed three times with Et₂O (500 mL). The combined organic layers were washed with 800 mL of saturated solution of sodium chloride, dried over MgSO₄, filtered,

26. On page 34, replace lines 3-14 with

B24
Example 4: Synthesis of (4,5-dihydrolMES)(PCy₃)Cl₂Ru=CHPh (formula 3). The ligand salt 1,3-dimesitylimidazolium tetrafluoroborate (2.94 g, 7.46 mmol, 1.2 equiv) was suspended in 50 mL of THF in a 250 mL round-bottom flask. This mixture was then treated with a solution of potassium *tert*-butoxide (840 mg, 7.49 mmol, 1.2 equiv) in 50 mL of THF via cannula at 22 °C. This mixture was immediately cannula transferred (20 mL THF used as rinse) to a second vessel containing a solution of (PCy₃)Cl₂Ru=CHPh (2) (5.01 g, 6.09 mmol, 1.0 equiv) in 100 mL of benzene (additional stirring of the ligand salt mixture at 22 °C prior to exposure to the Ru-carbene often resulted in incomplete conversion to the desired product). The resulting mixture was refluxed at 80 °C for 30 min. and then cooled to 22 °C. All manipulations from this point forward were carried out in air with reagent-grade solvents. The solvents were removed at reduced pressure, leaving a red-brown solid residue. The crude residue was dissolved in a minimal volume of 9:1 hexanes: Et₂O and loaded onto a wide plug of silica gel.

27. On page 35 replace lines 1-18 with

B25
[¹H NMR (400 MHz, CDCl₃): δ 7.31 (s, 12H, mesityl *o*-CH₃), 1.90 (s, 6H, mesityl *p*-CH₃). ¹³C NMR (75 MHz, CDCl₃): δ 293.40, 220.29 (d, ¹J_{CN} = 76.2 Hz), 151.16, 151.11, 138.27, 137.49, 137.08, 135.06, 129.77, 127.78, 51.64 (d, ¹J_{CN} = 71.9 Hz), 31.30 (d, ¹J_{PC} = 15.6 Hz), 27.68 (d, ¹J_{CH} = 9.8 Hz), 26.07, 21.09, 20.86, 19.88. ³¹P NMR (162 MHz, CDCl₃): δ 161.90 (s, PCy₃). Anal. Calcd for C₄₆H₆₅Cl₂N₂PRu: C, 65.08; H, 7.72. Found: C, 65.18; H, 7.71.

Example 5: Synthesis of (4, 5-dihydrolMES)Cl₂Ru = CH - *o* - O - *i* - Pr C₆H₄ (formula 5). (4,5-dihydrolMES)(PCy₃)Cl₂Ru=CHPh (formula 3) (895 mg, 1.05 mmol, 1.03 equiv) and C₆H₅COCl (261 mg, 2.64 mmol, 2.59 equiv) were weighed into a 100 mL round-bottom flask in a

B25
glove box and dissolved in 20 mL of CH_2Cl_2 . 2-isopropoxystyrene (4) (166 mg, 1.02 mmol, 1.0 equiv) was cannulated into the resulting deep red solution in 20 mL of CH_2Cl_2 at 22 °C. The flask was equipped with a condenser and stirred at reflux for 1 h. From this point forth, all manipulations were carried out in air with reagent-grade solvents. The reaction mixture was concentrated in vacuo to a dark brown solid residue. The crude material was dissolved in a minimal volume of 2:1 pentane: CH_2Cl_2 and loaded onto a plug of silica gel. Elution with 2:1 pentane: CH_2Cl_2 and then 1:1 pentane: CH_2Cl_2 removed a bright green band from the column. The column was then washed successively with straight CH_2Cl_2 and Et_2O (light green/yellow bands elute). These three fractions were pooled and concentrated to a dark green solid. This material was passed through a second silica gel plug in 1:1 hexanes: CH_2Cl_2 (bright green band

28. On page 48, replace lines 7-19 with

B26
Example 18: Experimental Procedure for RCM Catalyzed by Dendritic [(4,5-dihydrolMES) $\text{C}_1_2\text{Ru}=\text{CH}-o-\text{O}-i-\text{PrC}_6\text{H}_3(\text{CH}_2)_2\text{COO}(\text{CH}_2)_3\text{Si}(\text{Me})_2(\text{CH}_2)_3\text{Si}$] $_4$ (formula 31).
Diene (11) (32.7 mg, 0.233 mmol, 1.0 equiv) was weighed into a 25 mL round-bottom flask and dissolved in 5 mL of CH_2Cl_2 (0.05 M). Dendritic catalyst 31 (12.4 mg, 0.00366 mmol, 0.016 equiv) was added as a solid and the solution was allowed to stir at 22 °C. TLC analysis after 2 h indicated completion of the reaction. Work-up procedures proceeded in air with reagent-grade solvents. The mixture was concentrated at reduced pressure and passed through a short plug of silica gel in 100% CH_2Cl_2 , affording (12) (20.4 mg, 0.1819 mmol, 78%) as a colorless oil (TLC R_f = 0.25 in 4:1 hexanes: Et_2O). The catalyst was then flushed off of the column with 100% Et_2O affording 12.3 mg (0.00363 mmol, 99%) of a green solid. Ru recovery on the dendrimer was assessed using ^1H NMR spectroscopy (400 MHz). Integration of the isopropoxy methine proton

B²⁶
for both metal-occupied (4.90 ppm) and metal-vacant (5.71 ppm) sites gave a ratio of 92:8
respectively, indicative of 8% metal loss.

29. On page 48, replace lines 20- 23 with

B²⁷
Example 19: Synthesis of an Immobilized Catalyst. This procedure allows
installment of the linker and the active metal complex in a single step. Treatment of the
compound **35** with a stoichiometric amount of (4,5-dihydroIMES)(PCy₃) Cl₂Ru=CHPh in the
presence of allylchlorodimethylsilane led to successful ring-opening cross metathesis and